

**95\* Randomised, double blind, placebo-controlled Phase III Study of Bronchitol (inhaled dry powder mannitol) in Cystic Fibrosis (CF)**

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The airways in CF are characterised by a reduction in the water content of the airway surface liquid (ASL) and accumulation of thick mucus that is a precursor for chronic infection, inflammation and tissue damage. Inhaled mannitol is an osmotic agent that increases the water content of the ASL, improves mucociliary clearance and in studies has shown to improve lung function, lung hygiene and be well tolerated [1,2]. This phase III study was designed to assess the efficacy and safety of inhaled mannitol over the longer term.

**Methods:** The study was a randomised, double-blind, parallel, placebo-controlled design, where subjects inhaled 400 mg mannitol or control, twice daily for 6 months, with a further option of participating in a 6–12 month open label phase. Patients had confirmed CF, were >6 yrs with an FEV<sub>1</sub> ≥30 and <90% predicted, and were not using hypertonic saline.

**Demographics:** Preliminary baseline data were available for the 295 eligible patients. Patients were aged 6–56 yrs (mean 22 yrs) with 44.5% female and mean BMI of 21.33 kg/m<sup>2</sup>. The baseline % predicted FEV<sub>1</sub> was 62.0±16.44% and 55% of the patients were taking rhDNase.

**Objectives:** The primary endpoint was change in FEV<sub>1</sub>. The study was also powered to assess the change in FEV<sub>1</sub> in the group of patients taking rhDNase. Secondary endpoints included pulmonary exacerbations, quality of life, and antibiotic treatment.

**Results:** The 6 month blinded study completed in March 2009. This will be the first presentation of the CF-301 study results.

**Reference(s)**

[1] Robinson M, et al. Eur Respir J 1999; 14: 687–685.

[2] Jaques A, et al. Chest 2008; 133: 1388–1396.

Supported by: Pharmaxis Ltd, Australia.

**96\* Safety/Efficacy of Inhaled Human Alpha-1 Antitrypsin (AAT) in CF: A Phase II Clinical Study**

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Neutrophilic inflammation in CF is associated with excessive Neutrophil Elastase (NE) levels, which cause further damage to the respiratory tissue. The major antagonist of NE is AAT. In CF, the unregulated inflammatory process overwhelms the normal NE/AAT balance, leading to accumulation of NE in the lung and ultimately to tissue damage. The rationale for inhaled AAT therapy is to treat this imbalance and prevent further damage to the lung tissue by reducing the severity of this destructive cycle. Recently, a high purity, liquid, ready-to-use AAT was developed (Kamada Ltd., Israel) for inhalation using the eFlow<sup>®</sup> electronic nebulizer (PARI Pharma, Germany). The aim of this phase II study was to assess the safety and efficacy of inhaled AAT in CF patients.

**Study design:** Double-blind, randomized, placebo-controlled, repeated dose. Study method: 21 patients were randomized (2:1) to receive inhaled 80 mg active AAT or placebo once a day. The study comprised three treatment periods, 1 day, 7 days and 28 days. Safety and efficacy variables were tested.

**Results:** All patients completed the study without SAEs. One patient reported mouth dryness probably related to the study drug. A decrease in the absolute sputum neutrophil counts and in sputum NE levels was observed in the AAT group, but not in the placebo group.

**Conclusion:** Kamada AAT is safe and well tolerated when inhaled daily for 28 days. The reduction of neutrophils and NE detected in sputum suggests an anti-inflammatory effect in CF patients. Further clinical trials are warranted to evaluate the effects of inhaled AAT on disease progression.

Supported by: Kamada Ltd. Israel.

**97\* Final results of a 14- and 28-day study of VX-770 in subjects with CF**

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This randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, pharmacokinetics, and efficacy of VX-770, a CFTR potentiator, in adults with CF and at least one G551D-CFTR allele. Part 1 was a cross-over design in which subjects were randomized to receive placebo (n=4) or VX-770 q12 h at either 25 and 75 mg (n=8) or 75 and 150 mg (n=8) doses in two 14-day periods separated by a washout. Part 2 included distinct subjects from Part 1 randomized to placebo (n=4), 150 mg VX-770 (n=8), or 250 mg VX-770 (n=7) q12 h for 28 days. Most subjects (82%) were G551D/F508del-CFTR compound heterozygotes. VX-770 was generally well-tolerated at all doses and no subject withdrew from treatment. Most adverse events were mild or moderate in severity and no drug-related serious adverse events were reported. Within-subject comparisons showed statistically significant changes from baseline at Day 14 (Parts 1 and 2) and Day 28 (Part 2) for FEV<sub>1</sub>, sweat chloride, and nasal potential difference (NPD) zero chloride plus isoproterenol response in the VX-770 75, 150, and 250 mg dose groups. At Day 28 in subjects in the VX-770 150 mg dose group, the median relative change from baseline in FEV<sub>1</sub>%pred was +8.7% (range 2.2, 31.3; p<0.01), and absolute change from baseline in sweat chloride was -59 mmol/L (-66, -19; p<0.02) and NPD was -3.5 mV (-8.2, 0.5; p<0.02). These results suggest that further evaluation of VX-770 is warranted.

Supported by: CFRT, US FDA, Vertex.

**98\* Pharmacological characterization of a novel water-soluble activator of F508del-CFTR**

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One of the major therapeutic strategy in Cystic Fibrosis (CF) aims to develop modulators of CFTR (CF Transmembrane conductance Regulator) channels. Previously, we identified a new family of water-soluble and non-toxic CFTR inhibitors: the methylglyoxal-alpha-aminoazaheterocycle adducts (Routaboul et al; JPET 2007). Interestingly, in a structure-activity relationship study, some of them, like GPact-11a, were found positive as CFTR potentiator.

Firstly, using in vitro, ex vivo and in vivo techniques we demonstrated that GPact-11a is an activator of wt-CFTR (EC<sub>50</sub> = 5 μM). Indeed GPact-11a potentiates the forskolin-induced iodide efflux. Furthermore, by recording short-circuit current, we found that GPact-11a induced a CFTR<sub>inh</sub>-172 inhibited chloride secretion in cfr<sup>+/+</sup> mice. Then, in vivo, we observed an increase of the salivary secretion in the presence of GPact-11a in cfr<sup>+/+</sup> mice, but not in cfr<sup>-/-</sup> mice. Using the potential-sensitive probe oxonol, the effect of GPact-11a on F508del-CFTR rescued by miglustat was assessed by single-cell fluorescence imaging. We demonstrated that GPact-11a not only potentiates the forskolin induced response but more importantly activates alone the rescued F508del-CFTR.

To conclude, this work identifies, using in vitro, ex vivo and in vivo experiments, a novel activator of CFTR: GPact-11a. This agent, non-toxic and water-soluble, represents a good candidate, alone or in combination with a F508del-CFTR corrector, for the development of a pharmacologic therapy in CF.

Supported by: Mucovie 66, Vaincre la mucoviscidose, and CNRS.